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Abstract: Abnormal activation of hedgehog pathway signaling is a key driver in the pathogenesis of basal cell carcinoma (BCC). Vismodegib, a first-in-class small-molecule inhibitor of hedgehog pathway signaling, is approved by regulatory authorities for the treatment of adults who have metastatic BCC or locally advanced BCC that has recurred after surgery, or who are not candidates for surgery and who are not candidates for radiation. A second inhibitor, sonidegib, was also recently approved for the same patient group with locally advanced BCC. Adverse events (AEs) commonly observed in hedgehog pathway inhibitor (HPI)-treated patients include muscle spasms, ageusia/dysgeusia, alopecia, weight loss, and asthenia (fatigue). These AEs are thought to be mechanistically related to inhibition of the hedgehog pathway in normal tissue. Although the severity of the majority of AEs associated with HPIs is grade 1-2, the long-term nature of these AEs can lead to decreased quality of life, treatment interruption, and in some cases discontinuation, all of which might affect clinical outcome. The incidence, clinical presentation, putative mechanisms, and management strategies for AEs related to HPIs in advanced BCC are described. These observations represent the first step toward the development of mechanism-based preventive and management strategies. Knowledge of these AEs will allow health care professionals to provide appropriate counseling and supportive care interventions, all of which will contribute to improved quality of life and optimal benefit from therapy. **IMPLICATIONS FOR PRACTICE** The hedgehog pathway inhibitors (HPIs) vismodegib and sonidegib represent a therapeutic breakthrough for patients with advanced basal cell carcinoma. However, the nature of the low-grade adverse events (AEs) commonly observed in HPI-treated patients, including muscle spasms, ageusia/dysgeusia, alopecia, weight loss, and fatigue, can impact clinical outcomes as a result of decreased quality of life and treatment discontinuation. The incidence, clinical presentation, putative mechanisms, and management strategies for AEs related to administration of HPIs are described, with the goal of enabling health care professionals to provide appropriate counseling and supportive care interventions to their patients.

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Characterization and Management of Hedgehog Pathway Inhibitor-Related Adverse Events in Patients With Advanced Basal Cell Carcinoma

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Key Words. Adverse events • Management • Vismodegib • Sonidegib • Advanced basal cell carcinoma • Hedgehog pathway

ABSTRACT

Abnormal activation of hedgehog pathway signaling is a key driver in the pathogenesis of basal cell carcinoma (BCC). Vismodegib, a first-in-class small-molecule inhibitor of hedgehog pathway signaling, is approved by regulatory authorities for the treatment of adults who have metastatic BCC or locally advanced BCC that has recurred after surgery, or who are not candidates for surgery and who are not candidates for radiation. A second inhibitor, sonidegib, was also recently approved for the same patient group with locally advanced BCC. Adverse events (AEs) commonly observed in hedgehog pathway inhibitor (HPI)-treated patients include muscle spasms, ageusia/dysgeusia, alopecia, weight loss, and asthenia (fatigue). These AEs are thought to be mechanistically related to inhibition of the hedgehog pathway in normal tissue.

Although the severity of the majority of AEs associated with HPIs is grade 1–2, the long-term nature of these AEs can lead to decreased quality of life, treatment interruption, and in some cases discontinuation, all of which might affect clinical outcome. The incidence, clinical presentation, putative mechanisms, and management strategies for AEs related to HPIs in advanced BCC are described. These observations represent the first step toward the development of mechanism-based preventive and management strategies. Knowledge of these AEs will allow health care professionals to provide appropriate counseling and supportive care interventions, all of which will contribute to improved quality of life and optimal benefit from therapy. *The Oncologist* 2016;21:1–12

Implications for Practice: The hedgehog pathway inhibitors (HPIs) vismodegib and sonidegib represent a therapeutic breakthrough for patients with advanced basal cell carcinoma. However, the nature of the low-grade adverse events (AEs) commonly observed in HPI-treated patients, including muscle spasms, ageusia/dysgeusia, alopecia, weight loss, and fatigue, can impact clinical outcomes as a result of decreased quality of life and treatment discontinuation. The incidence, clinical presentation, putative mechanisms, and management strategies for AEs related to administration of HPIs are described, with the goal of enabling health care professionals to provide appropriate counseling and supportive care interventions to their patients.

INTRODUCTION

Abnormal activation of hedgehog pathway signaling, observed in >90% of cases of basal cell carcinoma (BCC) [1, 2], is a key driver in the pathogenesis of BCC. Although the majority of

BCCs can be successfully treated with surgery, topical agents, or radiation, hedgehog pathway inhibition has been a therapeutic breakthrough for patients with advanced

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disease (locally advanced BCC [laBCC] or metastatic BCC [mBCC]; it is estimated that metastatic disease develops in <1% of patients) [1, 2]. Vismodegib was the first hedgehog pathway inhibitor (HPI) to be approved for the treatment of adults who have mBCC or laBCC that has recurred after surgery or who are not candidates for surgery and are not candidates for radiation treatment (approval granted by the U.S. Food and Drug Administration [FDA] in January 2012 [3] and the European Medicines Agency [EMA] in July 2013 [4]). In 2015, a second HPI (sonidegib) was approved by both the FDA and the EMA for patients with laBCC, based on data from the Basal Cell Carcinoma Outcomes with LDE225 Treatment (BOLT) study [5].

The safety profile of vismodegib is consistent within clinical trials and general clinical practice [6–12]. Commonly observed adverse events (AEs) include muscle spasms, ageusia/dysgeusia, alopecia, weight loss, and asthenia (fatigue). Similarly, the most commonly observed AEs in sonidegib-treated patients in the BOLT study included muscle spasms, alopecia, dysgeusia, nausea, increased blood creatine kinase level, asthenia, and weight loss [5]. Many of these AEs are thought to be mechanistically related to inhibition of the hedgehog pathway. Although the majority of AEs associated with HPIs are grade 1–2, they tend to be long-term and interfere with patient quality of life (QOL), leading to treatment interruption and discontinuation that may preclude the intended therapeutic effect. Therefore, appropriate strategies for the prevention and management of AEs are essential to ensure that patients can continue to receive and benefit from HPI treatment.

The Hedgehog Signaling Pathway

The hedgehog signaling pathway is critical for normal embryonic development and patterning [2]. In normal cells, the canonical hedgehog signaling pathway is activated by the binding of hedgehog ligands to their receptor protein patched homolog 1 (Patched; PTCH1). Ligand binding relieves the inhibitory effects of PTCH1 on the Smoothened protein (SMO). Signal transduction by SMO leads to activation and nuclear translocation of Gli transcription factors and induction of target genes, many of which are involved in proliferation, survival, and differentiation. In addition to the canonical signaling pathway, several noncanonical hedgehog signaling pathways have been identified [13, 14]. Inappropriate reactivation of the hedgehog signaling pathway can result in tumorigenesis, and it was first described in basal cell carcinoma nevus syndrome (BCCNS), also known as Gorlin syndrome [15–17]. In BCC, the hedgehog signaling pathway is typically activated by mutations that lead to dysfunction of the *PTCH1* gene, seen almost universally in patients with BCCNS and in most patients with sporadic BCC tumors. An estimated 80%–90% of sporadic BCC tumors have *PTCH1* mutations, whereas 10% harbor *SMO* mutations. Both types of mutations lead to constitutive SMO signaling and BCC development [2].

Although hedgehog signaling is silenced in most normal adult tissues, it has been shown to play a role in the repair of damaged tissues, the promotion of stem cell proliferation, and the regulation of maintenance of various tissues, including muscle, hair, taste buds, and the reproductive system [1, 18].

After injury, sonic hedgehog (Shh) signaling is reactivated in adult skeletal muscle and plays a functionally important role in regeneration by regulating injury-induced angiogenesis and myogenesis [19]. Pathway inhibition impairs production of angiogenic factors, decreases muscle blood flow, and reduces capillary density after injury [19]. Hedgehog signaling has been shown to regulate development and maintenance of taste buds and seems to play a critical role in taste function integrity [20, 21]. Adult mice treated with vismodegib display significant reductions in taste-bud size and number of taste cells, and decreased behavioral responses to sweet and bitter stimuli [21]. Interestingly, hedgehog-responding cells were lost in fungiform papilla epithelium in sonidegib-treated mice, with taste-bud remnants entirely absent or severely decreased in >90% of aberrant papillae [22]. The hedgehog signaling pathway is also active in the hair follicle, transitioning hair from the telogen (resting) to the anagen (active growth) phase of the growth cycle [23–25]. Shh-null mice (in which the *Shh* gene has been knocked out) exhibit follicles arrested at the hair germ stage of development [23, 24]. In mice, transient overexpression of Shh by gene transfer or topical application of a hedgehog agonist induces resting hair follicles to enter anagen, resulting in hair growth [25, 26]. Antibodies that block the activity of Shh are able to prevent hair growth in adult mice [27].

HPI Safety Profile

HPI safety data are available from a number of key studies (Table 1) [5–12]. Nearly all patients treated with HPIs experience at least one treatment-emergent AE (TEAE), with an incidence rate of 95%–100% observed across studies. In the RegiSONIC disease registry, protocol specified-related AEs were reported in 82% of the first 109 patients with laBCC given vismodegib [6–11]. The most frequent AEs observed with HPIs include muscle spasms, alopecia, dysgeusia, weight loss, asthenia, nausea, decreased appetite, and diarrhea (Table 2) [5–12]. The majority of AEs are mild or moderate (grade 1–2) and occur early in the course of treatment [6–11]. Reported rates of discontinuation because of all AEs vary across studies (e.g., 5% in the 12-week operable BCC study [11] and 36% in the Study of Vismodegib in Patients With Locally Advanced or Metastatic Basal Cell Carcinoma (STEVIE) [median duration of treatment 36.4 weeks] [12]). In addition, data from the ERIVANCE BCC 30-month analysis [8] and the STEVIE study [12] show that the severity of AEs did not worsen with longer treatment duration. Reasons for discontinuation vary depending on the type of advanced BCC; patients with laBCC are more likely to request discontinuation because of AEs, whereas patients with mBCC often discontinue because of disease progression [6]. However, it has been observed that patients who discontinued because of a grade 1 or 2 AE often experience complete or partial response before discontinuation [12]. It may be that some patients discontinue vismodegib when a response has been achieved and if the grade 1–2 AEs (considered “annoying”) are significantly impacting QOL. A similar safety profile was reported with sonidegib in the BOLT study [5] and in the subsequent 18-month follow-up [28]. There is a clear need to educate health care professionals (HCPs) and patients regarding AE management strategies that allow patients to continue treatment.

Table 1. Overview of key hedgehog pathway inhibitor studies providing safety data

Trial	Design	Treatment	Population	Primary objective	Analyses
ERIVANCE BCC	Single-arm, open-label, pivotal phase II study	Vismodegib 150 mg once daily	aBCC (N = 104)	Objective response rate	<ul style="list-style-type: none"> • Primary analysis [6] • 12-month analysis [7] • 30-month (final) analysis [8]
U.S. EAP	Single-arm, open-label, U.S.-based expanded access study	Vismodegib 150 mg once daily	aBCC (N = 119)	To provide access to vismodegib before commercial availability	Final analysis [9]
STEVIE	Single-arm, open-label phase II study	Vismodegib 150 mg once daily	aBCC (N = 1,227)	Incidence of AEs	Interim analysis of 499 patients with potential to be followed up for ≥ 12 months [12]
RegiSONIC	Prospective, observational U.S.-based disease registry	Clinician standard of care	aBCC; (109 patients with laBCC treated with vismodegib: September 11, 2015)	Describe real-world treatment patterns and outcomes associated with aBCC	Interim analysis of the first 109 patients with laBCC treated with vismodegib (clinical cutoff date September 11, 2015) [10]
Operable BCC	Nonrandomized, open label, three-cohort phase II study	Continual vismodegib 150 mg once daily for 12 weeks followed by surgery (cohort 1) Continual vismodegib 150 mg once daily for 12 weeks, followed by 24 weeks of observation, then surgery (cohort 2) Intermittent vismodegib 150 mg once daily (8 weeks on/4 weeks off/8 weeks on) followed by surgery (cohort 3)	Operable BCC (N = 74); cohort 1 (n = 24), cohort 2 (n = 25), cohort 3 (n = 25)	Complete histologic clearance rate	Final analysis [11]
BOLT	Multicenter, randomized, double-blind, phase II study	200 mg or 800 mg oral sonidegib daily	aBCC (N = 230); 200 mg (n = 79) and 800 mg (n = 151 ITT; n = 150 safety)	Objective response rate	Primary analysis [5]

Abbreviations: aBCC, advanced basal cell carcinoma; AE, adverse event; BOLT, Basal Cell Carcinoma Outcomes with LDE225 Treatment; EAP, expanded access program; laBCC, locally advanced BCC; STEVIE, Study of Vismodegib in Patients With Locally Advanced or Metastatic Basal Cell Carcinoma.

Prevention and Management Strategies for HPI-Related Adverse Events

Because the majority of AEs emerge early in treatment, patient education is key in terms of what to expect and the possible management options. It is recommended that physicians follow their local prescribing information. Treatment interruption is a common approach, and HCPs and patients should be encouraged to continue supportive care interventions after re-exposure. A thorough baseline examination is also important, including an evaluation of comorbidities (i.e., alopecia, myopathies, diabetes, gastrointestinal/liver disease, and sensory and motor neuropathies) and concomitant medications that might contribute to tolerability issues (e.g., glucose-lowering or diarrhea-causing agents, or neurotoxic, hepatotoxic, or myotoxic medications). Finally, the AEs and their associated management strategies (Figs. 1, 2; Table 3) [29] should be considered in the context of the benefit of HPI treatment and the rapid clinical response. Because most of the AEs induced by HPIs have a significant subjective component, it would be important to include questions specific to these untoward events during clinical evaluations. Although a

patient-reported outcomes questionnaire was recently developed for use in patients with BCC (Advanced Basal Cell Carcinoma Index) [30], it is not specific for AEs related to HPIs. Preliminary studies have yielded a questionnaire that, although it has not been validated, addresses some of the most common HPI toxicities and their impact on patient QOL (Fig. 3). This questionnaire would be useful in routine clinical care of patients treated with HPIs and in supportive care trials.

Muscle Spasms

In general, intensity of HPI-related muscle spasms is mild or moderate. Muscle spasms tend to occur more frequently at night and in the muscles of the lower leg and foot, although they can occur in any location. The impact of muscle spasms is compounded given their high incidence (50%) in elderly individuals [31]. They are thought to occur as a result of paradoxical activation of the noncanonical SMO/ Ca^{2+} /AMPK axis and inhibition of the canonical SMO signaling pathway, resulting in an influx of Ca^{2+} into muscle cells and, subsequently, immediate muscle contraction [29]. Muscle spasms

Table 2. Summary of safety data from key hedgehog pathway inhibitor studies

Parameter	ERIVANCE BCC							BOLT [5] N = 230	
	Primary analysis [6] N = 104	12 months [7] N = 104	30 months [8] N = 104	EAP [9] N = 119	STEVIE [12] N = 499	RegiSONIC [10] ^{a,b} n = 109	Operable BCC [11] N = 74	200 mg, n = 79	800 mg, n = 150
Any AE, %	100	100	100	98	98	82	99	95	100
Muscle spasms	68	71	71	71	64	53	76	49	67
Alopecia	64	65	66	58	62	46	58	43	55
Dysgeusia	51	54	56	71	54	60 ^c	50	38	59
Weight loss	46	50	52	16	33	N/A	N/A	27	38
Fatigue	36	40	43	19	16	N/A	20	29	36
Nausea	29	33	33	19	16	N/A	18	33	45
Loss of appetite	23	27	28	N/A	25	N/A	11	19	31
Diarrhea	22	26	27	25	17	N/A	8	24	22
Median time to onset of AE									
Muscle spasms	N/A	1.89 months	N/A	37 days	2.83 months	36 days	N/A	N/A	N/A
Alopecia	N/A	3.38 months	N/A	87 days	5.55 months	105 days	N/A	N/A	N/A
Dysgeusia	N/A	1.8 months	N/A	41 days	6.51 months	51 days	N/A	N/A	N/A
Weight loss	N/A	6.13 months	N/A	175 days	N/A	N/A	N/A	N/A	N/A
Fatigue	N/A	2.79 months	N/A	42 days	N/A	N/A	N/A	N/A	N/A
Nausea	N/A	2.14 months	N/A	30 days	N/A	N/A	N/A	N/A	N/A
Loss of appetite	N/A	2.87 months	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Diarrhea	N/A	4.47 months	N/A	38 days	N/A	N/A	N/A	N/A	N/A
Median duration of treatment, months	9.8	12.9	12.9	5.5	8.4	N/A	2.8	8.9	6.5
Discontinued treatment, %	51	72	92	100 ^d	80	N/A	34	51	69
Due to AEs	12	17	21	4	36	19	5	20	32

^aVismodegib-treated patients with laBCC.^bData in the RegiSONIC column refer to vismodegib-related AEs.^cIncludes dysgeusia and ageusia.^dSponsor study termination was the primary reason for discontinuation (79 patients transitioned to commercial drug).

Abbreviations: AE, adverse event; BCC, basal cell carcinoma; BOLT, Basal Cell Carcinoma Outcomes with LDE225 Treatment; EAP, expanded access program; laBCC, locally advanced basal cell carcinoma; N/A, not available; RegiSONIC, An Observational Study of Treatment Patterns and Effectiveness and Safety Outcomes in Advanced Basal Cell Carcinoma and Basal Cell Carcinoma Nevus Syndrome Patients; STEVIE, Study of Vismodegib in Patients With Locally Advanced or Metastatic Basal Cell Carcinoma.

are typically the most frequently observed AE during HPI treatment (49%–76% of all patients) and usually occur early in the course of treatment (Table 2).

The recommended management algorithm is presented in Figure 2A. Patients should be advised to maintain adequate hydration and gentle physical activity while taking an HPI. Laboratory testing is not required, according to the vismodegib label, although for sonidegib, creatine kinase (CK) levels should be assessed before treatment and periodically as clinically indicated. Any additional laboratory testing is at the discretion of the treating physician. A number of nonpharmacologic approaches can be used for grade 1–2 muscle spasms, with anecdotal benefit reported with passive stretching (these techniques can be easily taught to the patient by a physical therapist) [32], heating therapy, cryotherapy (ice) [33],

exercise, massage, peripheral transcutaneous electrical stimulation (for localized cramps) [34], splinting of affected areas while sleeping, and changes in sleeping or sitting position [35]. Although hydration is frequently used, especially when cramps are associated with exercise, no formal evidence supports hydration as a mechanism to reduce cramping. A number of pharmacologic treatments may be used for initial grade 1–2 symptoms, including calcium channel blockers (i.e., amlodipine [36]), diltiazem [37], verapamil [38], sports drinks (those that replace electrolytes), and nerve stabilizers (e.g., gabapentin or pregabalin) [39]. Magnesium supplementation has also been studied, and only a small, nonsignificant difference has been reported in reducing the frequency of idiopathic cramping [40]. Lidocaine [41], levetiracetam [42], vitamin B complex [43], naftidrofuryl (not available in the United States)

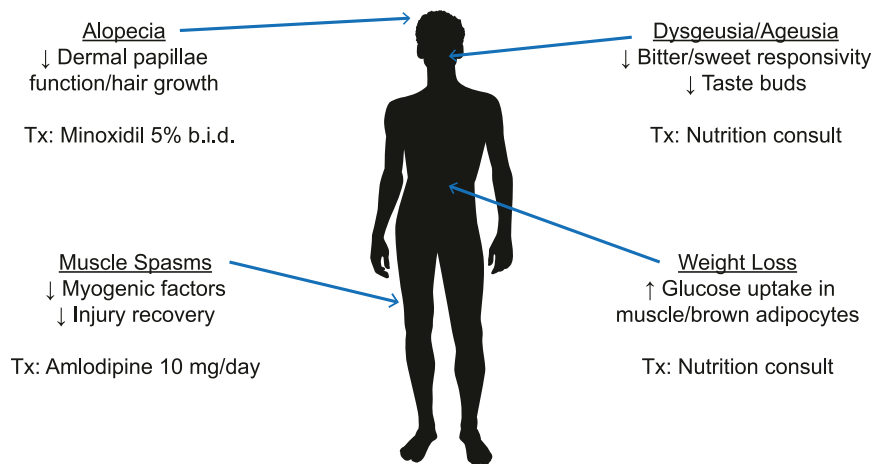


Figure 1. Adverse events associated with hedgehog pathway inhibitors [19, 21, 26, 29].
Abbreviations: b.i.d., twice daily; Tx, treatment.

[44], and cyclobenzaprine [45] have also all demonstrated effectiveness. For symptoms that have spread to the abdomen, calcium channel blockers (i.e., amlodipine) and antispasmodics (e.g., loperamide), antimuscarinic (e.g., trimebutine), or anticholinergic agents (e.g., scopolamine) may be useful. Although a number of agents, including vitamin E, baclofen, riluzole, L-threonine, xaliproden, indinavir, memantine, carbamazepine, and oxcarbazepine, have been investigated in patients with amyotrophic lateral sclerosis/motor neuron disease, none has shown any significant benefit in reducing cramping [46]. The FDA has advised against the use of quinine for cramps because of potentially dangerous and life-threatening side effects (QT prolongation, thrombocytopenia, and hypersensitivity reactions) [47], although, in non-U.S. countries, cautious use for severe cramps is permitted. The American Academy of Neurology recommends that quinine could be considered in select patients (i.e., in those whom cramps are disabling, no other agents relieve symptoms) after potential AEs are evaluated [48]. No adverse interactions have been reported with the use of HPIs and quinine.

For muscle spasms grade ≥ 3 reported during vismodegib treatment, experience indicates that at least two cycles of vismodegib treatment interruption (2–4 weeks each time) should be attempted before treatment discontinuation is considered. Anecdotal experience with use of a change in the dosing regimen (e.g., week on/week off) to mitigate spasms has also been reported. In the operable BCC study, most muscle spasms resolved within 6 weeks of treatment discontinuation [11]. Currently, a randomized, double-blind crossover study is recruiting patients to assess the effects of levocarnitine (vs. placebo) on the incidence and severity of vismodegib-related muscle spasms (ClinicalTrials.gov identifier NCT01893892). Limited information is available on sonidegib in this aspect, and there are no ongoing trials. The Muscle and Joint Measure (available from: https://www.fredhutch.org/content/dam/public/labs-projects/clinical-research/biobehavioral/MJM_updated_1-15-10_Syrjala_et_al_PDF.pdf) is a patient-reported outcomes tool used to measure musculoskeletal symptoms in cancer survivors and patients with spinal cord injuries, and it might be useful in assessment of the impact of muscle spasms and response to therapy [49, 50].

Taste Disturbances (Dysgeusia/Ageusia)

Severity of the loss (ageusia) or distortion (dysgeusia) of the sense of taste can range and can affect oral intake; it may even cause anorexia and depression. Gustation is important for QOL and can be affected by age, medication, and comorbidity [51]. Approximately 5% of the general population reports taste alterations, which increases progressively to 27% in those older than 80 years [52]. In patients with cancer, dysgeusia affects 56.3% of those treated with chemotherapy, 66.5% of those treated with radiotherapy, and 76% of those treated with combined chemotherapy and radiation [53]. In patients receiving chemotherapy, increased thresholds for bitter, sweet, sour, and salt tastes have been reported, whereas no difference has been reported for umami taste [54].

Hedgehog pathway signaling has been found to regulate differentiation and maintenance of taste buds [20, 55]. Vismodegib decreases the number of Shh-expressing type IV taste cells [21], which have been shown to be critical for taste-bud differentiation in adults. Taste disturbances occur in 50%–71% of vismodegib-treated patients, typically developing within the first few months of treatment (Table 2). In the sonidegib BOLT study, dysgeusia was reported in 38% and 59% of patients in the 200-mg and 800-mg groups, respectively [5]. Assessing taste changes in patients treated with HPIs may be challenging given the subjective nature; interestingly, a Taste and Smell Survey was used to evaluate improvement in chemosensory perceptions in a study of delta-9-tetrahydrocannabinol [56], and it might be useful in patients treated with HPIs.

When managing this particular AE, it is important to recognize that the symptoms may be independent of observed weight loss. The recommended management algorithm is presented in Figure 2B. Access to a nutritionist or dietitian at baseline and throughout treatment is beneficial [57], and the patient should be reminded to maintain adequate caloric intake and hydration. Dietary counseling has resulted in reduction in the occurrence of both early-onset and long-term dysgeusia. Similar effects were found with audiotapes and written information that was mailed to patients [53]. In addition, specific recipes given to patients, information on the use of flavor enhancers, and detailed nutritional information

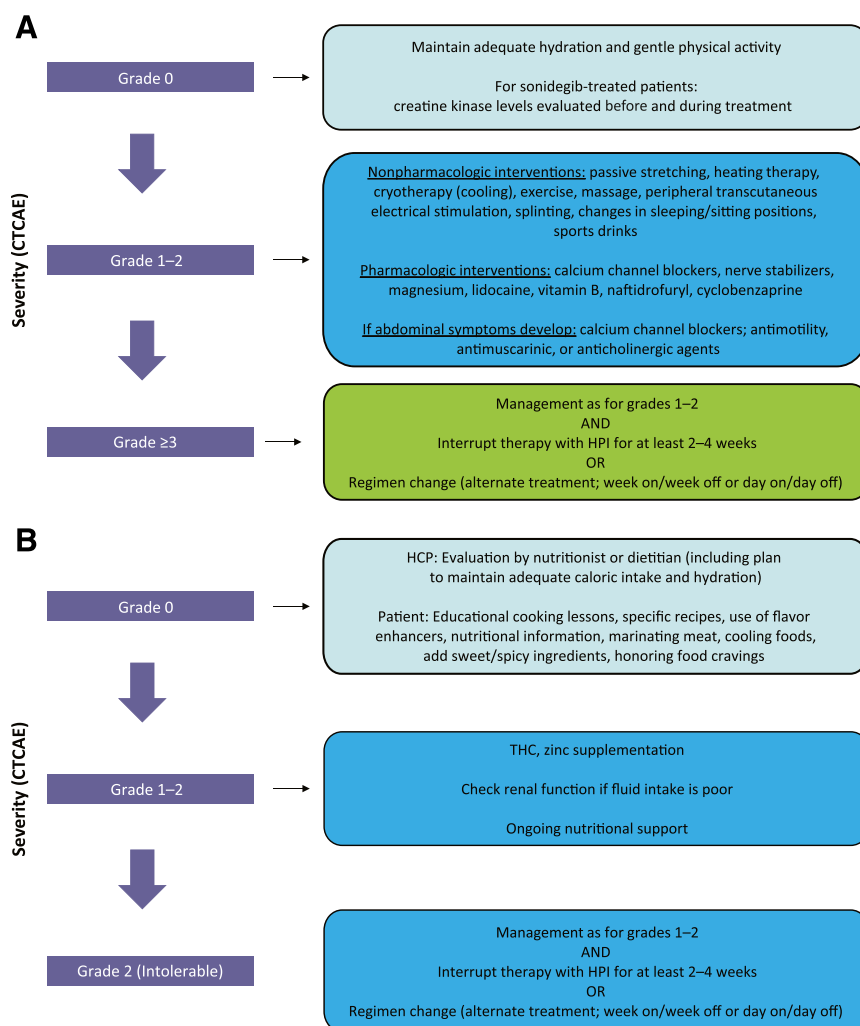


Figure 2. Proposed treatment algorithms based on anecdotal evidence discussed at the expert meeting. **(A):** Muscle spasms. **(B):** Taste disturbance. **(C):** Alopecia. **(D):** Weight loss. **(E):** Fatigue. Per CTCAE, for grade ≥3 events, at least 2 treatment interruptions (2–4 weeks) should be attempted before treatment discontinuation is considered.

Abbreviations: b.i.d., twice daily; CTCAE, Common Terminology Criteria for Adverse Events; DHT, dihydrotestosterone; HCP, health care professional; HPI, hedgehog pathway inhibitor; QD, once daily; THC, delta-9-tetrahydrocannabinol.

have resulted in better reporting of taste perception in patients receiving chemotherapy [58]. Strategies such as adding spicy ingredients, marinating meat, cooling foods, and adding sweet ingredients to meat have also been helpful. Cold foods seem to lessen metallic taste. Other helpful advice for patients, based on experience of the experts, included using new recipes, honoring specific food cravings, eating candy before meals, cutting food with lemon, using sweetened drinks, using plastic utensils, drinking from a straw, brushing the teeth and tongue before meals, and using a baking soda-salt wash or an antibacterial mouthwash. Given the half-life of HPIs and the life span of taste cells (10–24 days), it is likely the interruptions caused by dysgeusia require at least 4 weeks for recovery of gustation, although, in some cases, it can take as long as 6 months to return. Patients should attempt to restart HPIs if interruption is necessary.

A pilot study investigating delta-9-tetrahydrocannabinol compared with placebo in 24 patients with idiopathic dysgeusia showed improved chemosensory perception, food taste, appetite, and calories consumed [56]. In patients with idiopathic dysgeusia, zinc gluconate supplementation resulted

in improved taste ($p < .05$) [59]; however, contradictory results were seen in two studies of patients receiving radiotherapy for head and neck squamous cell carcinoma [60].

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Alopecia

There are approximately 100,000 hairs on the scalp, of which approximately 90% are in the anagen (growth) phase; the remainder are in the catagen (involuting or resting) and telogen (resting or quiescent) phases. Hair plays a critical role in the psychosocial well-being of patients, and its loss has been associated with decreased QOL, depression, and isolation. Alopecia with HPIs is usually characterized by diffuse loss of hair density

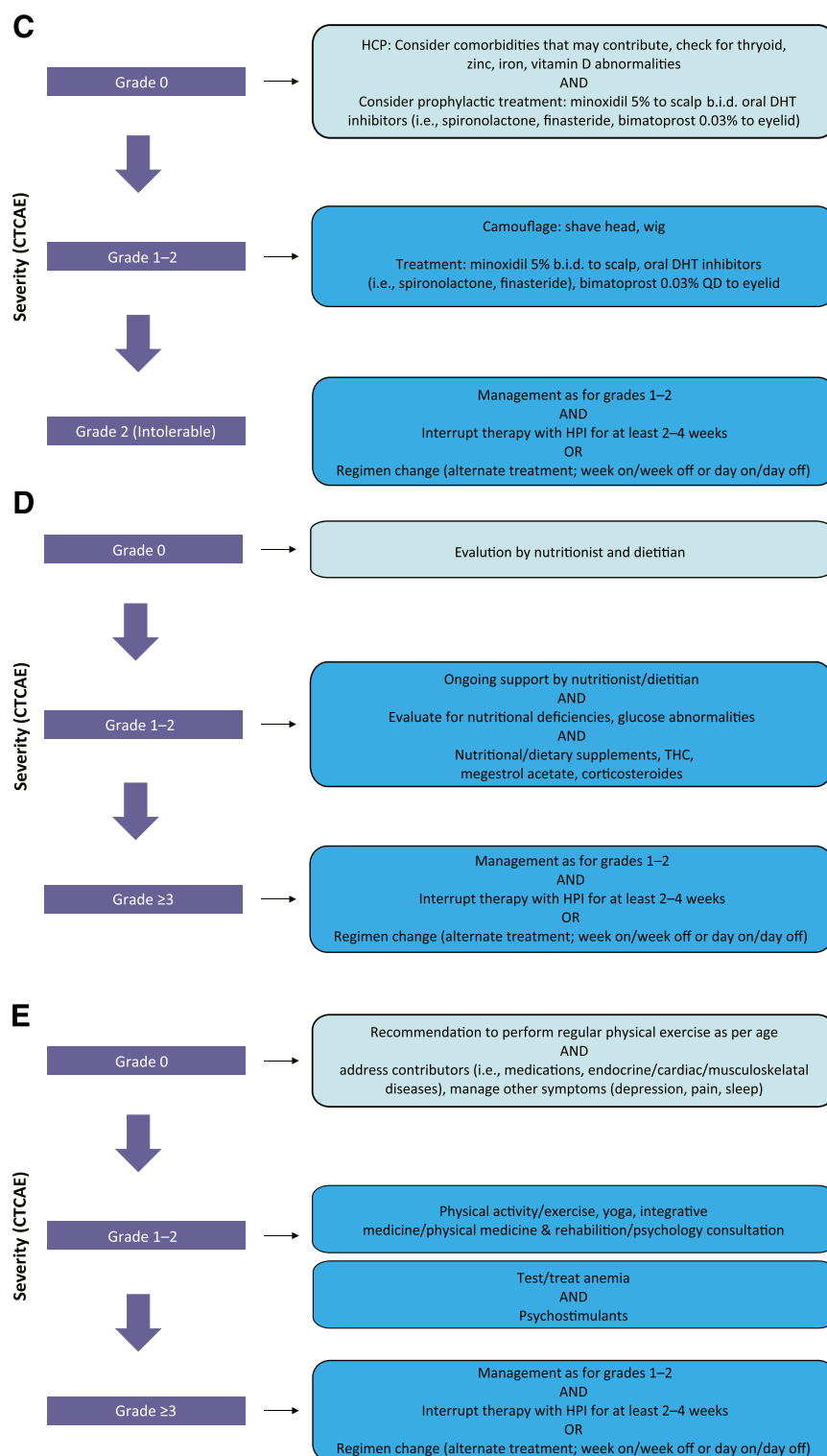


Figure 2. Continued.

over the entire scalp and may affect the eyebrows, eyelashes, and beard. Hair texture and quality is also often changed.

Hedgehog pathway inhibitors are thought to induce alopecia by preventing follicles from transitioning to the anagen phase after shedding of hair in the telogen phase [61]. Alopecia occurs in 46%–66% of vismodegib-treated patients and has a longer time to onset than is observed with cytotoxic

chemotherapy, developing after at least 2 months of treatment (Table 2). In the sonidegib BOLT study, alopecia was reported in 43% and 55% of patients in the 200-mg and 800-mg groups, respectively [5]. The severity of alopecia can be exacerbated because of the normal development of alopecia (40%–70% of individuals) as part of the aging process. The psychosocial impact of alopecia as reported by a patient can be captured

Table 3. Summary of drugs and doses for prevention or treatment of some of the hedgehog pathway inhibitor-related AEs

Symptom treated	Drug	Indication	Dose	Administration method
Muscle spasms	Amlodipine	High blood pressure and chest pain	Up to 10 mg/day	Oral
Muscle spasms	Gabapentin	Postherpetic neuralgia in adults; adjunctive therapy in treatment of partial-onset seizures	300–900 mg/day (can be titrated up to 1,800 mg/day) (neuralgia) 300–600 mg t.i.d. (seizures)	Oral
Muscle spasms	Pregabalin	Neuropathic pain associated with diabetic peripheral neuropathy; postherpetic neuralgia; partial-onset seizures; fibromyalgia; neuropathic pain associated with spinal cord injury	100 mg t.i.d. (diabetic peripheral neuropathy); 75–150 mg b.i.d. or 50–100 mg t.i.d. (postherpetic neuralgia); 150–600 mg/day (seizures); 300–450 mg/day (fibromyalgia); 150–600 mg/day (neuropathic pain associated with spinal cord injury)	Oral
Muscle spasms	Cyclobenzaprine	Adjunct to rest and physical therapy for relief of muscle spasms associated with acute, painful musculoskeletal conditions	5 mg t.i.d. May be increased to 10 mg t.i.d.	Oral
Diarrhea	Loperamide	Diarrhea; reduce amount of stool in individuals with an ileostomy	2 mg up to 8–16 mg/day	Oral
Diarrhea	Trimebutine	Symptoms of irritable bowel syndrome	200 mg t.i.d.	Oral
Nausea and vomiting	Scopolamine	Sedative and tranquilizing depressant to the central nervous system	1.5 mg every 3 days	Transdermal
Alopecia (eyelashes)	Bimatoprost	Increasing thickness, length, and darkness of eyelashes	One drop (0.03%) along the skin of the upper eyelid every evening	Topical
Alopecia	Finasteride	Male pattern alopecia	1 mg/day in men; 5 mg/day in women	Oral
Alopecia	Minoxidil	Male and female pattern alopecia	5% one to two times daily	Topical
Nausea	Ondansetron	Nausea and vomiting	8 mg b.i.d.	Oral
Weight loss, nausea	Tetrahydrocannabinol	Anorexia, nausea	Capsules every evening	Oral
Weight loss	Fish oil	Weight loss	12 tablets (consisting of 18% EPA and 12% DHA) daily	Oral
Nausea and weight loss	Metoclopramide	Nausea and vomiting, anorexia	10 mg four times daily	Oral
Weight loss	BCAA supplementation	Anorexia	BCAA 4.8 g t.i.d. (leucine 2.36 g, isoleucine 1.28 g, and valine 1.16 g)	Oral
Weight loss	Megestrol acetate	Anorexia	Initiate at 160 mg daily up to a maximum of 800 mg daily	
Weight loss	Corticosteroids	Nausea and vomiting	Prednisone, 5 mg t.i.d. Dexamethasone, 3–6 mg daily	

Abbreviations: AE, adverse event; BCAA, branched-chain amino acid; b.i.d., twice daily; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; t.i.d., three times daily.

using the Hairdex questionnaire [62]. In the interim analysis of the STEVIE study, treatment was discontinued because of alopecia in 4.2% of patients [12]. In the operable BCC study (cohort 2: 12 weeks of vismodegib and 24 weeks of observation), most cases of alopecia (13 of 17 patients) resolved within 24 weeks of treatment discontinuation [11]. Interestingly, alopecia with use of vismodegib might be more pronounced and longer lasting in patients with BCCNS [63]. Patients should be reminded that the alopecia is unlike that caused by traditional cytotoxic chemotherapy. Alopecia typically develops gradually, and, in some cases, can be delayed and actually occur after HPI treatment has been halted. Alopecia associated with HPI treatment can also be persistent and, in rare cases, might be permanent [64]. Supportive care includes the identification of comorbidities that might contribute to alopecia and use of minoxidil, oral dihydrotestosterone

inhibitors (i.e., spironolactone, finasteride), and camouflaging methods (i.e., sprays, powders, hairpieces, and wigs) (Fig. 2C).

Weight Loss

Cancer-related weight loss occurs frequently and may be associated with the underlying disease, depression, or therapy. An international consensus defined cancer anorexia-cachexia as a multifactorial syndrome, with weight loss >5% over the past 6 months or weight loss >2% in individuals already showing depletion [65]. Weight loss was reported in approximately 50% of patients in the ERIVANCE BCC analyses [6–8], with lower incidence (33%) observed in the real-world STEVIE study [12]. In the BOLT study, weight loss was reported in 27% and 38% of patients in the 200-mg and 800-mg sonidegib groups, respectively [5]. Onset is generally seen 6 months

BCC-Treatment Symptoms Checklist (BCC-TSC)

Please circle or mark one number per line to indicate your response as it applies to the last 7 days.

	Not at all	A little bit	Some- what	Quite a bit	Very much
I have a good appetite.....	0	1	2	3	4
I have hair loss.....	0	1	2	3	4
I have muscle cramps.....	0	1	2	3	4
I have problems tasting food and drink.....	0	1	2	3	4
I feel fatigued.....	0	1	2	3	4
I am losing weight.....	0	1	2	3	4
I have loose watery stools (diarrhea).....	0	1	2	3	4
I feel nauseous.....	0	1	2	3	4

Figure 3. BCC treatment symptoms checklist for hedgehog pathway inhibitor-associated adverse events.
Abbreviation: BCC, basal cell carcinoma.

after the start of treatment [7]. Although muscle mass is often lost, there does not seem to be a correlation between weight loss and taste disturbances, and body weight typically returns to previous levels after treatment interruption. Ongoing evaluations by a nutritionist can be helpful, and supplements can be useful for patients at risk for weight loss (including elderly individuals; those with low body mass index or significant comorbidities; or those who live alone). Vismodegib administration can be interrupted for up to 8 weeks, followed by discontinuation if necessary (Fig. 2D).

Asthenia

Asthenia (or fatigue) is defined by the National Comprehensive Cancer Network (NCCN) as a distressing, persistent, and subjective sense of physical, emotional, or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and that interferes with usual functioning [66]. In HPI-treated patients, asthenia can also be influenced by a number of factors, including interrupted sleep patterns because of muscle spasms, or decreased caloric intake because of taste disturbances. Patients should be assessed and treated appropriately for depression and questioned about general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue. NCCN guidelines recommend patient education (especially at the start of treatment), together with physical activity, yoga, other physical-based therapies, psychosocial interventions, nutritional consultation, sleep therapy, and management of comorbidities (e.g., pain, insomnia, depression) [66]. Provider-directed National Cancer Institute recommendations also include the use of psychostimulants, along with anemia treatment, cognitive behavioral therapy, and rest [67]. Although there is little evidence to support the use of pharmacologic intervention

(e.g., methylphenidate) [68, 69], because depression and HPI-induced fatigue are concomitant factors in patients with advanced BCC, these agents might play a role. Self-report instruments to measure fatigue are available [70], and the American Society of Clinical Oncology published guidelines for the management of fatigue in cancer survivors that might be useful [71]. The proposed management algorithm is presented in Figure 2E.

Nausea

Nausea is often the first AE to be reported and it can be challenging to manage. Vismodegib and sonidegib are considered moderate to highly emetogenic oral antineoplastic agents by the NCCN, and NCCN guidelines for the prevention or oral chemotherapy-related antiemesis include the use of serotonin inhibitors, to be started before initiation and continued daily. For breakthrough emesis, recommendations are based on adding one agent from a different drug class to the current regimen and, if emesis is controlled, continuing on a schedule. Breakthrough agents include the atypical antipsychotic olanzapine, the benzodiazepine lorazepam, cannabinoids (such as dronabinol and nabilone), phenothiazines, steroids, and others, such as haloperidol, metoclopramide, and scopolamine [72]. Patient education is important so patients know what to expect during treatment. Nonmedical interventions include taking vismodegib at nighttime or with food. Gastrointestinal motility medications (e.g., domperidone) or anti-nausea medications (e.g., dimenhydrinate), are useful medical interventions. Drugs that alter the pH of the upper gastrointestinal tract (e.g., proton pump inhibitors, H₂-receptor antagonists, and antacids) might alter the solubility of vismodegib and reduce bioavailability. However, results of a clinical study did not show clinically significant pharmacokinetic interaction between vismodegib and rabeprazole (a proton pump inhibitor) in healthy volunteers

(unpublished data; Roche). If symptoms do not improve, treatment interruption or a change in dosing regimens should be the next step, with discontinuation as the final option.

Other AEs

Components of the hedgehog signaling pathway play a functional role in the ovaries of mature rodents [73, 74], and, in phase I and II trials, amenorrhea or irregular menses occurred in 10 of 35 premenopausal female patients (28.5%) treated with vismodegib [75]. Resolution of amenorrhea in some patients has been observed after discontinuation of vismodegib. HPis can affect female fertility; consequently, fertility preservation strategies should be discussed with women of childbearing age before starting treatment with HPis. HPis are teratogenic in animals and, in humans, can result in embryo-fetal death or severe birth defects. Pregnancy status should be verified before treatment with HPis in women of childbearing potential, and patients should be informed of the need for contraception.

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For sonidegib-treated patients, CK levels should be assessed before treatment and periodically as clinically indicated. Additional laboratory testing is at the discretion of the treating physician. Elevated CK levels were observed in 29% and 37% of patients treated with sonidegib 200 mg and 800 mg, respectively [5]. Patients starting therapy with sonidegib must be informed of the risk for muscle-related AEs, including rhabdomyolysis. Patients should be carefully monitored during treatment and advised to promptly report any unexplained muscle pain, tenderness, or weakness. Patients with neuromuscular disorders and those in whom sonidegib is administered in combination with agents that can increase the risk for muscle toxicity (e.g., 3-hydroxy-3-methylglutaryl-coenzyme [HMG-CoA] reductase inhibitors) should be followed up carefully. According to the vismodegib label, laboratory testing for CK level is not necessary.

CONCLUSION

Hedgehog pathway inhibitors could be an important treatment option for patients with advanced BCC—a population for whom options were previously limited. The safety profile of vismodegib was consistent during long-term follow-up and across a number of clinical trials. Although the severity of the AEs typically associated with treatment is mostly grade 1 or 2, the long-term nature of these AEs can lead patients to discontinue treatment. Moreover, patients with complete response to HPis tend to discontinue treatment because of these common AEs more frequently than patients with no response or with partial response, who might discontinue only because of more severe AEs. Evidence also suggests that changing HPis will not lead to significantly different AEs, underscoring the importance of maintaining patients on therapy with the first

HPI administered and providing sufficient support to manage AEs to maximize effectiveness.

Assessing the QOL of patients treated with HPis is critical because discrepancies have been seen in how HCPs and patients grade the severity of AEs [76]. A patient-reported outcomes questionnaire has been developed for patients with advanced BCC and BCCNS; however, this questionnaire is not specifically designed to capture AEs unique to HPis [30]. A symptom questionnaire has been developed for use in vismodegib-treated patients (Fig. 3), and its use might aid in ascertaining the impact of these events in patient QOL and aid in supportive care interventions. Studies in BCC populations are ongoing to further explore an optimal dosing regimen for vismodegib [77, 78]. In addition, data indicate that the safety profile of vismodegib is comparable in elderly patients and younger patients [79]. To ensure maximum benefit from therapy, use of the management recommendations presented here might enable HCPs to maintain QOL in patients taking HPis.

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